STABLE LIPOPHILIC EMULSIONS FOR ACRYLIC COATING AND METHOD OF MAKING

BACKGROUND OF THE INVENTION

The present invention relates to stable lipophilic emulsions. More particularly, the present invention relates to stable lipophilic emulsions which may be stored and shipped for use with polymers comprised of acrylic and methacrylic acid, their alkyl esters and their alkyl amino alkyl esters for the coating of pharmaceutical dosage forms.

In the past, the coating of pharmaceutical dosage forms utilizing acrylic and methacrylic acid, their alkyl esters and their alkyl amino alkyl esters usually required the addition of talc to prevent the coating from being sticky and causing defects by tablets sticking to each other or the coating equipment. The sticking together of tablets and their separation causes deformities in the coating which are referred to in the art as "picks" when the pharmaceutical dosage forms such as tablets or capsules are separated.

More recently, in U.S. Pat. No. 5,292,522 - Petereit et al. describe the usefulness of a lipophilic material to replace talc in the coating composition. Petereit et al. elaborate on this coating process in Petereit et al., "Glycerol Monostearate as a Glidant in Aqueous Film-Coating Formulations", European Journal of Pharmaceutics and Biopharmaceutics, Volume 41, No. 4, pages 219-228 (1995). However, the coating method utilizing glycerol monostearate is difficult to practice due to the

difficulty in preparing the lipophilic material for incorporation into the polymer emulsion. All of the examples disclosed by Petereit et al. disclose the preparation of a low solids emulsion of the lipophile, such as glycerol monostearate at 2%, at the time of coating. Also, preparation of the most useful dispersions use an emulsion stabilizer at about 40% of the lipophile. The emulsion stabilizer, a surface active ingredient, at this level may have an adverse effect on the permeability of the film. Further, since the lipophilic emulsion is not stable for periods more than several hours, the lipophilic emulsion must be prepared as a part of the process of coating the pharmaceutical dosage forms and this preparation requires heating of the ingredients, dispersing the ingredients and then cooling the dispersion before incorporation into the coating suspension. This is a cumbersome preparation process at the manufacturing and coating facility and this process of preparing the lipophilic emulsion during the coating process creates difficulties which manufacturers would like to avoid.

SUMMARY OF THE INVENTION

In accordance with the present invention, a lipophilic emulsion may be prepared at a high concentration and stabilized such that it may be stored and shipped and may be presented for use in the coating suspension at the time of coating with no heating, homogenizing or cooling.

In accordance with the present invention, a lipophile, such as glycerol monostearate, may be dispersed in water at high concentration and stabilized.

In accordance with the present invention, any quantity of lipophile may be delivered from a stable emulsion concentrate to facilitate coating suspension

preparation.

In accordance with the present invention, lipophiles may be chosen from glycerol monostearate (GMS), glycerol monooleate, glycerol monolaurate, propylene glycol monolaurate, propylene glycol monooleate, propylene glycol monostearate, sorbitan monooleate, sorbitan monostearate, other glycerides including diacetylated monoglyceride and vegetable oils such as corn or coconut oils.

In accordance with the present invention, stable lipophilic emulsions may be prepared with emulsion stabilizer by weight of between 1% and 5% of the lipophile.

In accordance with the present invention, emulsion stabilizers which may be used include polysorbate 80 (PS 80), sodium lauryl sulfate and polysorbate 60.

In accordance with the present invention, plasticizers may be included in the emulsion. The plasticizers may include triethyl citrate (TEC), triacetin (TA), glycerin, propylene glycol (PG) and polyethylene glycol (PEG 400-8000 MW).

Briefly and basically, the present invention comprises an emulsion wherein a lipophile is chosen from the group consisting of glycerol monostearate, glycerol monooleate, glycerol monolaurate, propylene glycol monolaurate, propylene glycol monooleate, propylene glycol monostearate, sorbitan monooleate, sorbitan monostearate, diacetylated monoglyceride and vegetables oils. An effective amount of an emulsion stabilizer such as polysorbate 80 is used. An effective amount of an emulsion stabilizer may be by weight between 1% and 5% of the lipophile. The lipophile and the emulsion stabilizer are homogenized to form micelles having a size of 50 microns or less. This emulsion is stable for a period of at least three months.

Briefly, in accordance with the method of the present invention, an emulsion of a water insoluble lipophile is produced by bringing the water to a temperature of between 60 and 80 degrees centigrade, adding the lipophile, adding an emulsion stabilizer, stirring vigorously for approximately 5 minutes, passing the mixture through a homogenizer for between about 10 to 120 minutes and cooling the emulsion to room temperature while stirring. The 10 to 120 minutes corresponds to 3 to 10 passes of the formulation through a homogenizer or, in other words, 3 to 10 cycles.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, a lipophile such as glycerol monostearate, can be dispersed in water at high concentrations to prepare stable emulsions that can be stored and shipped for later use with emulsions of polymers comprising acrylic acid and methacrylic acid, their alkyl esters and their alkyl amino alkyl esters for coating pharmaceutical dosage forms without having to prepare a lipophilic emulsion at the coating location.

Lipophiles that may be utilized in practicing the invention include, in addition to glycerol monostearate, glycerol monooleate, glycerol monolaurate, propylene glycol monolaurate, propylene glycol monooleate, propylene glycol monostearate, sorbitan monooleate, sorbitan monostearate, as well as other glycerides such as diacetylated monoglyceride (i.e. Myvacet 9-45, commercially available from Quest International, 5115 Sedge Boulevard, Hoffman Estates, Illinois, 60192), and vegetable oils such as corn and coconut oils. The stable lipophilic emulsions may be used directly with the acrylic polymers without any heating, homogenizing or cooling to

form the lipophilic emulsion. Any quantity of lipophile may be delivered from a stable lipophilic emulsion concentrate to facilitate coating suspension preparation.

In accordance with the present invention, stable dispersions or emulsions of the various lipophiles may be prepared with an emulsion stabilizer such as polysorbate 80 using only an amount of the emulsion stabilizer which is 1% to 5% of the weight of the lipophile. Other emulsion stabilizers may be used including sodium lauryl sulfate and polysorbate 60.

In accordance with the present invention, the lipophilic emulsion remains stable with the use of plasticizers in the suspension. The plasticizers may include triethyl citrate (TEC), triacetin (TA), glycerin, propylene glycol (PG) and polyethylene glycol (PEG 400-8000 MW). These dispersions can be added to all of the acrylic resin copolymer dispersions. Some acrylic copolymers are available as dry 100% powders, for example, Eudragit L100, commercially available from Rohm America LLC, 2 Turner Place, Piscataway, NJ 08855. Such acrylic copolymers need to be dispersed into water before adding the lipophilic emulsion to produce the coating composition.

The following is an example of a lipophilic emulsion in accordance with the present invention.

EXAMPLE 1

MATERIAL	QUANTITY	
Glycerol Monostearate (GMS)	10.00kg	
Triethyl Citrate (TEC)	9.60	(20.00% solids)

Polysorbate 80 (PS80)	0.40
Water	80.00

In preparing the lipophilic emulsion of Example 1, water was charged to a 50 gallon tank and heated to 70 degrees centigrade with stirring. The triethyl citrate and polysorbate 80 were added and the temperature was raised to 70 degrees centigrade. The glycerol monostearate was sprinkled onto the surface of the water slowly allowing it to melt and to be incorporated into the suspension. The mixture was stirred vigorously with a propeller mixer. The mixture was passed through an in-line homogenizer for 15 minutes, recirculating into the stirred batch. The suspension was inspected under a microscope at 100 magnification and the emulsion contained micelles of about 10 microns. The homogenizer was turned off and the batch was cooled with stirring to 30 degrees centigrade.

The homogenizer utilized in preparing Example 1 was manufactured by Silverson Machines, Inc., 355 Chestnut Street, East Longmeadow, MA 01028. The mixture should be passed through the in-line homogenizer for 3 to 10 cycles and it is believed that it is important to produce micelles of 50 microns or less in order to produce the stability of the emulsion desired by the invention. The 3 to 10 cycles would take from 10 to 120 minutes. The emulsion produced is stable for at least three months and this allows adequate time for packaging, storage and distribution to manufacturers and use by the manufacturer in the coating process.

Preservatives may be added and the lipophilic emulsion may be packaged for

storage and distribution to manufacturers in the pharmaceutical industry for use in connection with acrylic coating processes. The emulsion may be shipped concentrated and effectively diluted by the coater at the time of coating.

The lipophilic emulsion of Example 1 may be used in various acrylic resin copolymer coatings, a specific example is illustrated in Example 2.

EXAMPLE 2

MATERIAL	QUANTITY	
USP/NF methacrylic acid copolymer (30%)	60 parts	
Lipophilic emulsion of Example 1	10	(20% solids)
Water	30	

The methacrylic acid copolymer emulsion (i.e. Eudragit L30D55 commercially available from Rohm America LLC) and water were added to a container and stirred at room temperature. The lipophilic emulsion of Example 1 was added with stirring and stirred for one hour. This enteric coating suspension was ready for spraying in a fluid bed coater or side vented coating machine. This is a very desirable, simplified procedure for making a coating suspension using acrylic copolymers with a pre-emulsified lipophile. The coating suspension may be colored if desired by stirring in a dispersion of any of the FD&C, D&C or uncertified colorants approved for use in the pharmaceutical industry. Uncertified colorants include titanium dioxide, iron

oxides, other minerals and natural colors.

Additional examples of stable lipophilic emulsions are as follows.

EXAMPLE 3

MATERIAL	QUANTITY	
GMS	15.0kg	
TEC	9.8	(25% solids)
PS80	0.2	
Water	75.0	

EXAMPLE 4

MATERIAL	QUANTITY	
GMS	19.8	
PS80	0.2	(20% solids)
Water	80.0	

EXAMPLE 5

MATERIAL	QUANTITY	
Glycerol Monooleate	10.0	
TEC	9.8	
PS80	0.2	(20% solids)
Water	80.0	

EXAMPLE 6

MATERIAL	QUANTITY	
Sorbitan Monostearate	10.0	
PEG 400	9.8	
PS80	0.2	(20% solids)
Water	80.0	

EXAMPLE 7

MATERIAL	QUANTITY	
GMS	10.0	
TEC	9.9	
PS80	0.1	(20% solids)
Water	80.0	

In accordance with the present invention, a wide variety of lipophilic materials may be emulsified for inclusion into acrylic coating emulsions.

Another example of the use of a lipophilic emulsion in an acrylic coating emulsion is shown in Example 8.

EXAMPLE 8

MATERIAL	QUANTITY	
Ammonium methacrylate copolymer (30%)	60.0	
Lipophilic emulsion of Example 7	6.0	(21.2% solids)
TEC	2.0	
Water	32.0	

This blend may be stirred for an hour and sprayed on tablets, capsules or granules in side vented pans or fluid bed columns.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification as indicating the scope of the invention.